

**Amendments to the Claims:**

The listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) A modified cytokine ligand polypeptide comprising a modified amino acid sequence which is a modification of the native cytokine amino acid sequence of said ligand, wherein the native amino terminal and carboxyl terminal amino acid residues of the native polypeptide are linked, directly or indirectly, together, characterised in that said ligand is provided with alternative amino terminal and carboxyl terminal amino acid residues and further wherein at least one binding domain for said ligand's cognate binding partner is disrupted.

2. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 1 wherein said ligand is selected from the group consisting of: growth hormone; leptin; erythropoietin; prolactin; tumour necrosis factor (TNF), interleukins (IL), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11; the p35 subunit of IL-12, IL-13, IL-15; granulocyte colony stimulating factor (G-CSF); granulocyte macrophage colony stimulating factor (GM-CSF); ciliary neurotrophic factor (CNTF); cardiotrophin-1 (CT-1); leukemia inhibitory factor (LIF); oncostatin M (OSM); interferon, IFN $\alpha$  and IFN $\gamma$ , osteoprotegerin (OPG),

3. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 2 wherein said ligand is growth hormone.

4. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 1 wherein said native amino terminal and carboxyl terminal amino acid residues are directly linked to each other.

5. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 1 wherein said native amino terminal and carboxyl terminal amino acid residues are indirectly linked by a linking molecule.

6. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 5 wherein said linking molecule is a peptide linker.

7. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 6 wherein said linking peptide is a flexible peptide linker.

8. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 7 wherein said flexible linker is a polypeptide which comprises 5 to 30 amino acid residues.

9. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 8 wherein the linker comprises 10 to 20 amino acid residues.

10. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 6 wherein said linker comprises at least one copy of the peptide: Gly Gly Gly Gly Ser.

11. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 5 wherein said linker is an inflexible linker.

12. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 11 wherein said linker comprises a  $\alpha$ -helical region.

13. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 1 wherein said a receptor binding domain of said ligand comprises a low affinity binding site.

14. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 13 wherein said low affinity binding domain is site 2 of growth hormone.

15. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 14 wherein said low affinity binding domain of growth hormone is between about amino acid 116 to amino acid 122 of human growth hormone as represented by the amino acid sequence shown in Figure 1.

16. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 15 wherein the alternative amino terminal and carboxyl

terminal amino acid residues are derived from between amino acid 116 and amino acid 122 of human growth hormone as represented by Figure 1.

17. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 16 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 118 and amino acid 121 of human growth hormone as represented by Figure 1.

18. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 16 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 119 and amino acid 121 of human growth hormone as represented by Figure 1.

19. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 16 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 120 and amino acid 121 of human growth hormone as represented by Figure 1.

20. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 16 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 118 and amino acid 120 of human growth hormone as represented by Figure 1.

21. (Previously Presented) A modified cytokine ligand polypeptide to Claim 16 wherein said alternative amino terminal and carboxyl terminal amino

acid residues are derived from between amino acid 119 and amino acid 120 of human growth hormone as represented by Figure 1.

22. (Previously Presented) A modified cytokine ligand polipeptide according to Claim 14 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between about amino acid 100 and amino acid 102 of human growth hormone as represented by the amino acid sequence shown in Figure 1.

23. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 14 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between about amino acid 130 and amino acid 132 of human growth hormone as represented by the amino acid sequence shown in Figure 1.

24. (Withdrawn-Previously Presented) An oligomeric cytokine ligand polypeptide comprising at least two modified cytokine ligand polypeptides according to Claim 1, wherein said ligands are linked, either directly or indirectly, together.

25. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 24 wherein said polypeptides are linked by a peptide linker comprising an  $\alpha$ -helical region.

26. (Withdrawn-Previously Presented) An oligomeric cytokine\_ ligand according to Claim 24 wherein said oligomer comprises two modified cytokine ligand polypeptides.

27. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 26 wherein said oligomer comprises, at least modified cytokine ligand polypeptides.

28. (Withdrawn-Previously Presented) An oligomeric cytokine\_ ligand according to Claim 26 wherein said oligomer comprises at least two modified growth hormone polypeptides.

29. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 28 wherein said oligomeric growth hormone polypeptide comprises multiple ligand polypeptides.

30. (Withdrawn-Previously Presented) An oligomeric cytokine\_ ligand according to Claim 24 comprising at least one modified cytokine ligand polypeptide according to Claim 1 linked, either directly or indirectly, to at least one native cytokine ligand polypeptide from which said modified cytokine ligand polypeptide was derived.

31. (Withdrawn-Previously Presented) An oligomeric cytokine\_ ligand according to Claim 24 wherein said modified cytokine ligand polypeptide

according to Claim 1 is linked to the extracellular ligand binding domain of said ligands cognate receptor.

32. (Withdrawn-Previously Presented) An oligomeric cytokine\_ ligand according to Claim 24 wherein said linker comprises a cleavage site.

33. (Withdrawn-Previously Presented) An oligomeric cytokine\_ ligand according to Claim 32 wherein said cleavage site is a proteolytic cleavage site.

34. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 33 wherein said cleavage site is sensitive to a serum protease

35. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 33 wherein said cleavage site comprises the amino acid sequence: LVPRGS, or functional variant thereof.

36. (Previously Presented) An oligomeric cytokine ligand according to Claim 33 wherein said cleavage site comprises at least one copy of the amino acid sequence: GGGGS, or functional variant thereof.

37. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 36 wherein said cleavage site comprises the amino acid sequence PGI(S).

38. (Withdrawn-Previously Presented) An oligomeric cytokine<sub>1</sub> ligand according to Claim 33 wherein said cleavage site comprises the amino acid sequence: LVGPRGSPGI.

39. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 36 wherein said cleavage site comprises at least two copies of the amino acid sequence GGGGS that flank said cleavage, site.

40. (Withdrawn-Previously Presented) An oligomeric cytokine ligand according to Claim 39 wherein said cleavage site is sensitive to the serum protease thrombin.

41. (Withdrawn-Previously Presented) An isolated nucleic acid molecule which encodes a modified cytokine ligand polypeptide according to Claim 1 or an oligomeric modified cytokine ligand polypeptide comprising at least two modified cytokine ligand polypeptides according to Claim 1, wherein said ligands are linked, either directly or indirectly, together.

42. (Withdrawn-Previously Presented) A vector comprising the nucleic acid molecule according to Claim 41.

43. (Withdrawn-Previously Presented) A host cell transfected or transformed with a nucleic acid molecule according to Claim 41 or a vector comprising the nucleic acid molecule of Claim 41.



44. (Withdrawn-Previously Presented) A host cell according to Claim 43 wherein said cell is a eukaryotic cell.

45. (Withdrawn-Previously Presented) A host cell according to Claim 44 wherein said cell is a mammalian cell, a yeast cell, an insect cell, or a plant cell.

46. (Withdrawn-Previously Presented) A host cell according to Claim 43 wherein said cell is a prokaryotic cell.

47. (Withdrawn-Previously Presented) A non-human transgenic mammal transfected or transformed with the nucleic acid molecule according to Claim 41 or a vector comprising the nucleic acid molecule according to Claim 41.

48. (Previously Presented) A pharmaceutical composition comprising the modified cytokine ligand polypeptide of Claim 1, an oligomeric form thereof, a nucleic acid molecule encoding the modified cytokine ligand polypeptide or oligomeric form thereof, a vector comprising the nucleic acid molecule encoding the modified cytokine ligand polypeptide or oligomeric form thereof, or a cell transformed with the nucleic acid molecule or the vector, in a pharmaceutically acceptable carrier.

49. (Withdrawn-Previously Presented) A screening method to generate modified cytokine ligand polypeptides according to Claim 1 comprising the steps of:

i) forming a preparation comprising native cytokine ligand polypeptide molecules wherein the native amino terminal and carboxyl terminal amino acids are linked either directly or indirectly together;

ii) generating modified cytokine ligand polypeptide molecules wherein said molecules have alternative amino terminal and carboxyl terminal amino acids; and

iii) testing the activity of said modified cytokine ligand polypeptides.

50. (Withdrawn-Original) A method according to Claim 49 wherein said native cytokine is growth hormone.

51. (Original) A modified cytokine ligand polypeptide identified by the method according to Claim 49.

52. (Original) A ligand according to Claim 51 wherein said modified cytokine ligand polypeptide is growth hormone.

53. (Withdrawn-Previously Presented) A method of treatment of subject comprising administering an effective amount the modified cytokine ligand polypeptide of Claim 1, an oligomeric form thereof, a nucleic acid molecule encoding the modified cytokine ligand polypeptide or oligomeric form thereof, a vector comprising the nucleic acid molecule encoding the modified cytokine ligand

polypeptide or oligomeric form thereof, a cell transformed with the nucleic acid molecule or the vector, or a combination thereof.

54. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 119 and amino acid 121 of human growth hormone as represented by Figure 1.

55. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 120 and amino acid 121 of human growth hormone as represented by Figure 1.

56. (Previously Presented) A modified cytokine ligand polypeptide according to Claim 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 118 and amino acid 120 of human growth hormone as represented by Figure 1.

57. (Previously Presented) A modified cytokine ligand polypeptide to Claim 17 wherein said alternative amino terminal and carboxyl terminal amino acid residues are derived from between amino acid 119 and amino acid 120 of human growth hormone as represented by Figure 1.